Development of the Reproductive System

Resources:
http://php.med.unsw.edu.au/embryology/
Larsen’s Human Embryology
The Developing Human: Clinically Oriented Embryology

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Lecture overview

Sex determination

Embryonic origins of the reproductive system

Gonad development

Development of the reproductive tract

Development of the external genitalia

Development of secondary sex characteristics

Disorders of sexual development

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Three factors that determine gender phenotype:

1. Genetic sex
   - chromosomal composition: XX or XY
   - determined at conception

2. Gonad and urogenital tract development
   - Development of testes or ovaries
   - Defined during embryonic development

3. Development of secondary sex characteristics
   - Hormone dependent
   - Defined during puberty
End product gastrulation:

Trilaminar embryo

Ectoderm (*Neural crest*)
- brain, spinal cord, eyes, *peripheral nervous system*
- epidermis of skin and associated structures,
  *melanocytes, cranial connective tissues (dermis)*

Mesoderm
- musculo-skeletal system, limbs
- connective tissue of skin and organs
  *urogenital system, heart, blood cells*

Endoderm
- epithelial linings of gastrointestinal and respiratory tracts
Embryonic tissues contributing to development of the reproductive system

- Intermediate Mesoderm
- Coelomic Epithelium
- Primordial Germ Cells

Week 4 embryo
Early Mesoderm Development

1: notochord
2: paraxial mesoderm
3: intermediate mesoderm
4: lateral plate mesoderm
Intermediate Mesoderm

Segmented and unsegmented intermediate mesoderm
Mesonephric duct
Urogenital sinus
Mesonephric tubules
Ureteric buds
Intermediate Mesoderm

3 nephric systems:
- Pronephros: regress
- Mesonephros: reproductive system, and collecting duct and tubules of the kidney
- Metanephros: nephrons of the kidney
Coelomic epithelium

Lateral plate mesoderm develops into:
- Splanchnic/visceral mesoderm
- Somatic/parietal mesoderm

Intraembryonic coelom: 3 cavities:
- Pericard
- Pleural
- Peritoneum
PGCs arise during gastrulation
PGCs are initially set apart in hindgut/yolk sac/allantois
Later the PGCs migrate into the genital ridges through the hindgut into the genital ridges
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Later the PGCs migrate into the genital ridges through the hindgut into the genital ridges

http://php.med.unsw.edu.au/embryology/images/2/26/Primordial_germ_cell_002.mp4
Intermediate mesoderm gives rise to urogenital system:

Ductal system develops within intermediate mesoderm

Three regions within intermediate mesoderm:
1. Pronephros: transient
2. Mesonephros:
   - forms mesonephric (Wolffian) duct
   - functional embryonic kidney
   - forms gonads
3. Metanephros:
   - duct forms ureteric bud
   - forms adult kidney

Mesonephros is covered by coelomic epithelium
Gonad development
Gonad Development
Bipotential organs

Genital Ridges
Somatic gonad cells
Germ cells
Wolffian/Mesonephric Duct
Mullerian duct/Paramesonephric duct

(From: Mouse development, Ch. Sex Determination and differentiation, Swain and Lovell-Badge)
Gonad Development
Bipotential tissues

Male:
- Testes
- Epididymus
- Vas deferens
- Seminal vesicle
- Ejaculatory duct and inputs:
  - Penis
  - Urethra

Female:
- Ovary
- Infundibulum
- Oviduct
- Ampulla
- Uterus
- Cervix
- Upper Vagina
- Lower Vagina
- Clitoris

Gonad Development
Bipotential tissues

Ductal systems in mesonephros:
- Wolffian duct
- Mullerian duct

Genital tubercle

Gonad
Gonad Development
Bipotential gonadal cells

- Sertoli cells
- Leydig cells
- Spermatogonia

Somatic gonad cells:
- Supporting cells
- Steroid-producing cells

Primordial germ cells

Granulosa cells
Theca cells

Oogonia
Gonad Development

Somatic gonad cells in XY gonad:
Sertoli cells first, then fetal Leydig cells
Fetal Leydig cells after birth replaced by adult Leydig cells

(Adapted from Ross and Capel, 2005)
Gonad Development

http://php.med.unsw.edu.au/embryology/images/7/7f/Testis_001.mp4
http://php.med.unsw.edu.au/embryology/images/7/7b/Ovary_001.mp4
Gonad Development

Embryonic testis

Embryonic ovary

Mesonephros

- Leydig cells
- Sertoli cells
- Germ cells
Gonad Development

Sex determination

Somatic gonad cells in XY gonad:
Sertoli cells first, then fetal Leydig cells
Fetal Leydig cells after birth replaced by adult Leydig cells

(Adapted from Ross and Capel, 2005)
Sry, the male sex determining gene

Y chromosome
Sry is transiently expressed in Sertoli Cells and induces SOX9 expression

Sry expression in XY genital ridges
Sry, the male sex determining gene

- Sry expression levels:
  - Sry: 10.5 to 11.5 dpc
  - Sox9: 11.5 to 12.5 dpc

- Genital ridge formation:
  - +SRY: Testis development
  - −SRY: Ovary development

- Sex determination:
  - +SRY: SOX9, Amh, FGF9, Other male genes
  - −SRY: WNT4, RSPO1, Follistatin, FOXL2

- Testicular and ovarian development:
  - Testis development:
    - FGF9
    - Amh
    - Other male genes
  - Ovary development:
    - WNT4, RSPO1, Follistatin
    - FOXL2

- Bipotential gonad:
  - Mesonephros
  - Genital ridge

- Time (dpc):
  - 10.5, 11.5, 12.5
Development of Reproductive Tract

Male:
- Testes

Wolffian Duct:
- Epididymus
- Vas deferens
- Seminal vesicle
- Ejaculatory duct
- Urethra

Female:
- Ovary

Mullerian Duct:
- Infundibulum
- Oviduct
- Ampulla
- Uterus
- Cervix
- Upper Vagina
Development of Reproductive Tract

- Sertoli cells produce anti-Müllerian hormone (AMH): Müllerian duct regression

- Leydig cells produce testosterone: Wolffian duct development into rete testis, epididymis and vas deferens.

- In absence of these hormones: loss of Wolffian duct, Müllerian duct develops female reproductive tract: oviduct and uterus

http://php.med.unsw.edu.au/embryology/images/7/7f/Testis_001.mp4
http://php.med.unsw.edu.au/embryology/images/7/7b/Ovary_001.mp4
http://php.med.unsw.edu.au/embryology/images/1/12/Uterus_001.mp4
### Development of the external genitalia

Embryonic genitalia are bipotential
**XY:** Dihydrotestosterone

<table>
<thead>
<tr>
<th>Bipotential tissue</th>
<th>XY</th>
<th>XX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cloacal membrane</td>
<td>Disappears</td>
<td>Disappears</td>
</tr>
<tr>
<td>Genital Tubercle</td>
<td>Glans penis</td>
<td>Clitoris</td>
</tr>
<tr>
<td>Genital Folds</td>
<td>Penis shaft</td>
<td>Labia minora</td>
</tr>
<tr>
<td>Genital swellings</td>
<td>scrotum</td>
<td>Labia majora</td>
</tr>
<tr>
<td>Urethral groove</td>
<td>Disappears</td>
<td>Vaginal opening</td>
</tr>
</tbody>
</table>

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**XY**
- Genital tubercle
- Genital fold
- Genital swelling

**XX**
- Labial swelling
- Labial swelling
- Scrotal swelling
- Scrotal swelling
- Labium major
- Labium minus
- Prepuce
- Glans penis
- Shaft of penis
- Urethral orifice
- Vaginal opening
- Anus
Development of the external genitalia

Urorectal septum separates rectum from urogenital sinus

XY:
Bladder and urethra
Prostate

XX:
Bladder and urethra
Uterus and vagina
Development of the external genitalia

Descent of Testes

Gubernaculum

Inguinal canal

Processus vaginalis

(a) 7-month fetus

Muscular wall of abdomen
Inguinal canal
Fascial covering of spermatic cord
Vaginal process
Penis

(b) 8-month fetus

Closed proximal portion of vaginal process
Spermatic cord
Tunica vaginalis
Cavity of tunica vaginalis
Scrotum
Gubernaculum

(c) 1-month old infant
Development of the external genitalia

Cryptorchidism
Development of secondary sex characteristics

Puberty

Male HPG Axis

- Hypothalamus
  - GnRH
  - Anterior pituitary
    - LH
    - FSH
    - Testes
      - Testosterone
        - Activation of sperm production
        - Masculinization
        - Hair growth

Female HPG Axis

- Hypothalamus
  - GnRH
  - Anterior pituitary
    - LH
    - FSH
    - Ovaries
      - Estrogen
      - Progesterone
        - Activation of menstrual cycle
        - Feminization
        - Hair growth
Development of secondary sex characteristics

Puberty

- development of secondary sexual characteristics
  - females
    - breast growth
    - growth of axillary and pubic hair
    - increase in size of pelvic outlet to prepare for childbirth
    - menarche – 1st menstrual bleeding
  - males
    - growth of scrotum, testes, and length of penis
    - growth of axillary and pubic hair
    - increased size of larynx and length of vocal cords – deeper voice
    - nocturnal emissions – discharge of semen during sleep
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Disorders of Sex Development

Sex reversal
- XX males: Transfer of Y chromosome into X chromosome
- XY females: androgen insensitivity syndrome/mutations in Sry/Sox9

Hermaphroditism
- Ambiguous external genitalia
- Gonads: both ovarian and testicular tissues: ovotestes

Hypospadias: Failure of genital folds to fuse

Cryptorchidism: Failure of testes to descent

Tract abnormalities: unicornate uterus, double uterus

Hydrocele: peritoneal fluid through processus vaginalis into scrotum
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